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RESEARCH ARTICLE

Outcome of patients with undifferentiated embryonal sarcoma of the liver treated according to European soft tissue sarcoma protocols

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Abstract

Background: To assess the outcomes of pediatric patients with undifferentiated embryonal sarcoma of the liver (UESL) and treatment including at least surgery and systemic chemotherapy.

Methods: This study included patients aged up to 21 years with a pathological diagnosis of UESL prospectively enrolled from 1995 to 2016 in three European trials focusing on the effects of surgical margins, preoperative chemotherapy, use of radiotherapy (RT), and chemotherapy.

Abbreviations: CI, confidence interval; EFS, event-free survival; IRS, Intergroup Rhabdomyosarcoma Study; IVA, ifosfamide, vincristine, and actinomycin-D; MMT95, Malignant Mesenchymal Tumour 95; NRSTS, Non-Rhabdomyosarcoma Soft Tissue Sarcoma; OS, overall survival; RT, radiotherapy; SIOP, International Society of Pediatric Oncology; STSC, Italian Soft Tissue Sarcoma Committee; UESL, undifferentiated embryonal sarcoma of the liver; VA, vincristine and actinomycin-D; VAIA, ifosfamide, vincristine, and actinomycin-D alternated with adriamycin.

Results: Out of 65 patients with a median age at diagnosis of 8.7 years (0.6–20.8), 15 had T2 tumors, and one had lymph node spread, 14 were Intergroup Rhabdomyosarcoma Study (IRS) I, nine IRS II, 38 IRS III, and four IRS IV. Twenty-eight upfront surgeries resulted in five operative spillages and 11 infiltrated surgical margins, whereas 37 delayed surgeries resulted in no spillages ($p = .0119$) and three infiltrated margins ($p = .0238$). All patients received chemotherapy, including anthracyclines in 47. RT was administered in 15 patients. With a median follow-up of 78.6 months, 5-year overall and event-free survivals (EFS) were 90.1% (95% confidence interval [CI]: 79.2–95.5) and 89.1% (95% CI: 78.4–94.6), respectively. Two out four local relapses had previous infiltrated margins and two out of three patients with metastatic relapses received reduced doses of alkylating agents. Infiltrated margins ($p = .1607$), T2 stage ($p = .3870$), use of RT ($p = .8731$), and anthracycline-based chemotherapy ($p = .1181$) were not correlated with EFS.

Conclusions: Multimodal therapy improved the outcome of UESL. Neoadjuvant chemotherapy for pediatric patients increases the probability of complete surgical resection. The role of anthracyclines and RT for localized disease remains unclear.

KEYWORDS
antineoplasic agents, liver, pediatrics, radiotherapy, sarcoma, surgical procedures

1 | INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is an uncommon hepatic tumor of mesenchymal origin, recognized as a unique clinicopathologic entity in 1978, and histologically characterized by spindle or stellate cells arranged in whorls and sheets, without any evidence of specific differentiation.[1] It accounts for 9%–13% of pediatric hepatic tumors, without gender predilection. Patients present at a median age of 8 years, but there is a wide range from 4 months to 19 years.[1–4] The typical clinical presentation includes abdominal pain associated with a mass that is at risk of bleeding or rupture. Sometimes a cystic and/or solid appearance on imaging can be misleading.[4,5]

Since its initial description when the reported survival was 38%, progress has been made through the adoption of multimodal strategies including chemotherapy, surgery, radiotherapy (RT), and in a few cases primary or rescue liver transplantation. More recent studies have reported overall survivals (OS) ranging from 50% to 100%.[1–3,6] Surgery forms the cornerstone of treatment. However, in European protocols, surgery is combined with soft tissue sarcoma chemotherapies and/or external beam RT, whereas this multimodal approach is not systematically used in North American studies, or in adult patients.[2,3,7,8] Metastatic disease is present in 13%–15% of the patients at diagnosis, usually involves the lungs, and is associated with worse survival.[3,7]

All studies have reported small numbers of patients with UESL, limiting the capacity to produce strong scientific recommendations.

Over the past three decades, European soft tissue sarcoma cooperative groups have attempted to standardize the treatment of pediatric sarcomas, including UESLs. The aim of our study is to assess the outcomes of patients with UESL treated according to successive European malignant mesenchymal tumor protocols focusing on the outcomes according to preoperative chemotherapy, and the use of RT.

2 | METHODS

This study includes patients with UESL prospectively enrolled in three European protocols: the Malignant Mesenchymal Tumour 95 (MMT95) study (1995–2005) coordinated by the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumors (MMT) Group, the RMS96 study (1996–2005) by the Associazione Italiana Ematologia Oncologia Pediatrica-Soft Tissue Sarcoma Committee (AIEOP-STSC), and the NRSTS (Non-Rhabdomyosarcoma Soft Tissue Sarcoma) 2005 (2005–2016) by the European pediatric Soft tissue sarcoma Study Group (EpSSG) that was formed by merging the MMT and STSC groups.

Eligibility criteria included age up to 21 years, a pathologically proven diagnosis of UESL, no previous treatment except for primary surgery, no pre-existing illness preventing treatment, no previous malignant tumors, and an interval between diagnostic surgery and systemic treatment less than 8 weeks. All participating centers were required to obtain written approval from their local authorities and ethics committees and written informed consent from the patient and/or from their parents or legal guardians.

Clinical staging was defined according to the TNM (Tumor, Node, and Metastasis) system, T1 or T2 according to the invasion of

contiguous organs, and N0/N1 according to diagnostic imaging assessment of lymph nodes. Tumors were also staged according to the Intergroup Rhabdomyosarcoma Study (IRS) clinical grouping, determined after initial surgery. Patients with clinical group I disease had completely resected tumors; group II patients had macroscopically resected tumors with microscopic residual disease at the primary site; group III patients had incomplete resection or biopsy with macroscopic residual disease; and patients with metastatic disease were designated as group IV.

The therapeutic strategy recommended in the three protocols was similar and was based on conservative surgery at diagnosis. Adjuvant chemotherapy was administered after tumor resection. When complete tumor resection was deemed not feasible or uncertain, a diagnostic biopsy was recommended, followed by neoadjuvant chemotherapy, and surgery reconsidered after tumor response evaluation. As the role of RT was not clear in UESL, the decision to use RT was left to the treating center. In the NRSTS 2005 protocol, the general recommendations for RT could be for: unfavorable tumor location/size or prognosis, initial or operative spillage, infiltrated postoperative margins, initial tumor extending beyond the organ of origin, and radiological unequivocal nodes.

The chemotherapy regimens included:

In the MMT 95 study, eight courses of VA (vincristine and actinomycin-D) or nine courses of IVA (ifosfamide, vincristine, and actinomycin-D) were used as adjuvant therapy for patients in IRS group I or II, respectively. Nine cycles of IVA or CEVAIE (carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide, and etoposide) were used for patients in IRS group III or IV, respectively.

In RMS 96, patients in IRS groups I and II received nine courses of IVA. The VAIA combination (ifosfamide, vincristine, and actinomycin-D alternated with doxorubicin) was used in IRS group III for a total of nine courses.

These regimens were also recommended in the NRSTS 2005 protocol with the possibility to use the more intensive IVADo (IVA plus concomitant doxorubicin for the first four cycles) instead of VAIA.

Chemotherapy response in patients with macroscopic residual disease after initial surgery or biopsy (IRS groups III and IV) was evaluated after three cycles (week 9) and at the end of the treatment (with further assessments at the clinicians' discretion) and was defined as complete response (CR): clinically or histologically confirmed complete disappearance of disease; partial response (PR): tumor volume reduction of more than 66%; minor response (MR): reduction greater than 33% but less than 66%; no response or stable disease (SD): less than 33% reduction in tumor volume; progressive disease (PD): any increase in tumor size of any measurable lesion or appearance of new lesions.

OS and event-free survival (EFS) were analyzed. EFS was calculated from the date of diagnosis to the time of the event or last follow-up if no events occurred. Tumor progression, relapse, the occurrence of second malignancy, or death due to any cause were considered for EFS. OS was measured from the date of diagnosis to death from any cause. Patients still alive at the end of the study were censored at the date of last observation.

Outcomes were analyzed according to: the TNM classification; negative surgical margins; IRS group; the type of surgery defined as upfront versus delayed (i.e., after chemotherapy) surgery; the type chemotherapy especially the use of anthracyclines, and the use of RT.

2.1 | Statistical analyses

Numeric results were reported with median and range. Qualitative data were analyzed using 2 × 2 tables, using double-sided nonparametric tests. The survival probability was computed utilizing the Kaplan–Meier method, and heterogeneity in survival among strata of selected variables was assessed using the log-rank test. The 5-year EFS and OS values were reported along with their 95% confidence intervals (CI). All data analyses were performed using the SAS statistical package (SAS 9.4; SAS Institute Inc., Cary, NC, USA). *p*-Values less than .05 were considered significant.

3 | RESULTS

Overall 65 children were registered in the three protocols, four (6.1%) of them were metastatic. The majority of patients ($N = 44$) were registered in the NRSTS 2005 protocol, 16 in MMT95, and five in RMS96.

Clinical characteristics of patients are reported in Table 1. Median age at diagnosis was 8.7 years [0.6–20.8]. Male to female ratio was 1.82, 95% CI: [1.09–3.06]. The largest tumor diameter ranged from 7 to 30.8 cm (median 15 cm). Metastatic sites were peritoneal in two patients, and lungs ± pleura in two others.

3.1 | Treatment (Figure 1)

Upfront tumor resection was attempted in 28 (43.1%) patients (23 IRS I–II, two IRS III, and three IRS IV), and resulted in negative margins in 17 (60.7%) patients including the three IRS IV patients, microscopically infiltrated margins in nine patients, and macroscopic residuum (R2) in two IRS III patients.

All patients underwent systemic treatment (see Table S1 for treatment according to protocols). As expected, anthracyclines were administered in 47 (72.3%) patients, with a significantly higher proportion in IRS group III–IV than IRS group I–II: 36/42 (85.7%) versus 11/23 (47.8%), respectively ($p = .0011$). Response to initial chemotherapy was evaluable in 36 (data were missing for one) out of 37 IRS III–IV patients with neoadjuvant chemotherapy. A tumor volume reduction was reported in 24 (66%) patients: one CR (2.8%), 13 PR (36.1%), and 10 MR (27.8%). SD was observed in 11 patients and PD in one. Tumor response was not associated with the administration of anthracyclines ($p = .3310$). After neo-adjuvant chemotherapy, 37 IRS III–IV patients had delayed surgery, with 34 (91.8%) patients achieving complete tumor resection (R0), which was significantly higher than the upfront surgery group ($p = .0238$). Intraoperative spillage occurred in

TABLE 1 Patients characteristics.

Protocol	*N* (%)	Upfront surgery	Delayed surgery	*p*-Value
NRSTS 2005	49 (75.4)	20	29	
MMT95/SIOP96	16 (24.6)	8	8	.5195
Age at diagnosis				
≤1 year	2 (3.1)	2		
1–9 years	39 (60)	14	25	
10–17 years	23 (35.4)	11	12	
≥18 years	1 (1.5)	1		.1502
Gender				
Female	23 (35.4)	9	14	
Male	42 (64.6)	19	23	.6344
Tumor invasiveness				
T1	50 (76.9)	21	29	
T2 (extension beyond organ of origin)	15 (23.1)	7	8	.7489
Primary tumor size				
>5 cm and <15 cm	35 (53.8)	18	17	
>15 cm	26 (40)	9	17	
>5 cm and unknown	4 (6.1)	1	3	.1911
Locoregional involvement				
N0	64 (98.5)	28	36	
N1	1 (1.5)		1	.9999
IRS group				
I	14 (21.5)	14		
II	9 (13.8)	9		
III	38 (56.5)	2	36	
IV	4 (6.2)	3	1	

Abbreviations: IRS, Intergroup Rhabdomyosarcoma Study; MMT95, Malignant Mesenchymal Tumour 95; NRSTS, Non-Rhabdomyosarcoma Soft Tissue Sarcoma; SIOP, International Society of Pediatric Oncology.

five out of 28 patients (17.8%), with upfront surgeries versus none in the 37 IRS III–IV groups ($p = .01190$). In four out of five patients, the spillage was described as minimal. The type of upfront or delayed surgery is described in Table S2. Regarding the details of the surgical procedure, we could get 31 (13 NRSTS 2005, two RMS96, and 16 MMT95) surgical reports out of 65 patients registered in the database: 24 were anatomical (14 hemihepatectomies, nine trisectionectomies, and one left lateral segmentectomy) versus seven nonanatomical (atypical bi-segmentectomies). One IRS III patient underwent a liver transplantation. Neither margins, events, nor OS were associated with anatomical versus atypical liver resection ($p = .2764$, .3612, and .5950) with the limitations of few numbers.

RT was administered to 15 (23.1%) children: the target being the primary tumor in five with a median dose of 41.4 Gy (20–45 Gy), the whole abdomen in seven with a median dose of 25 Gy (14–45 Gy boosted on primary site), metastatic sites in two patients (21 Gy peritoneum and missing dose in the lungs), and data were missing in one patient.

Characteristics of patients according to RT administration are displayed in Table S3. Patients with invasive tumors (T2) and those included in NRSTS 2005 were irradiated significantly more frequently than those with T1 disease or from the other trials. Three out of the five patients with tumor spillage during upfront surgery received RT (primary tumor one, whole abdomen two). Both patients with spillage without RT developed an event: one had a second tumor, the other a metastatic relapse (Table S4). Regarding patients with metastatic disease at diagnosis, all had anthracycline-based chemotherapy, two received RT to lung metastases, one received RT to the primary tumor site only, and one patient did not receive RT.

3.2 | Outcome

With a median follow-up of 78.6 months (range 27.4–167.7), 59 (90.8%) patients were alive: 57 in first CR and two in second CR. Relapses occurred in seven patients: locoregional in three, metastatic in three (all IRS group I), and both local and metastatic in the patient who had a liver transplantation. One additional child developed a second malignancy (Ewing sarcoma) 6.1 years after the UESL diagnosis

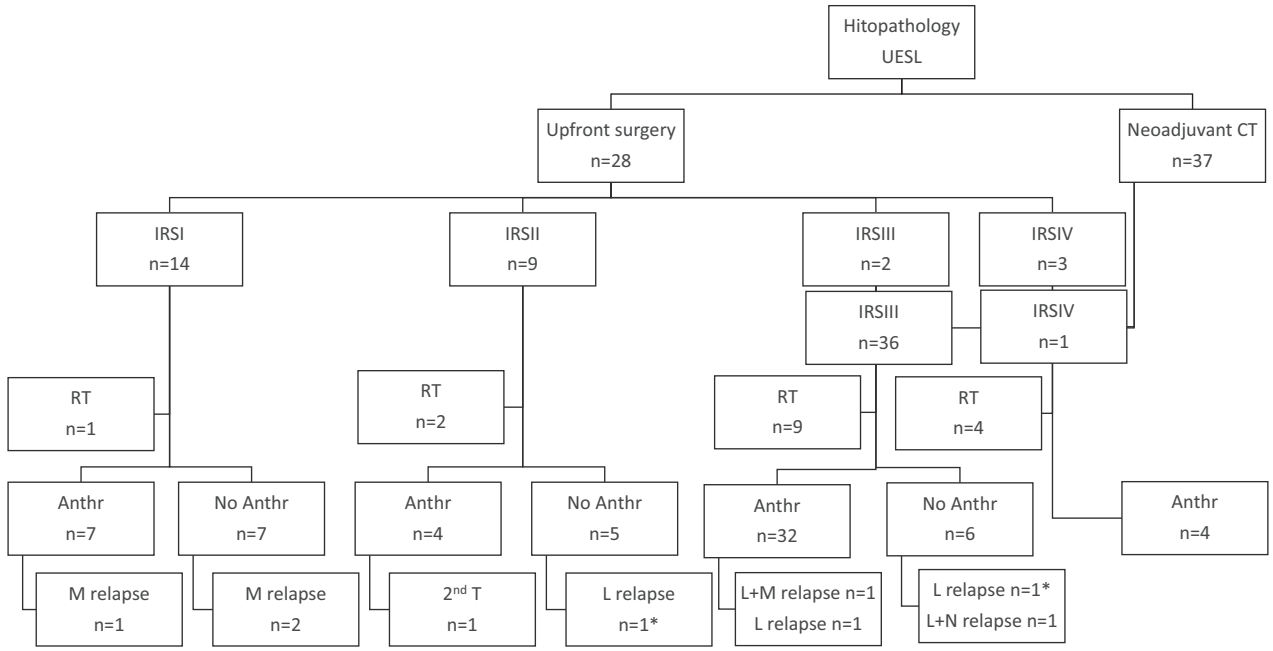

FIGURE 1 Flowchart of patients according to upfront versus delayed surgery, anthracyclines (Anthr), radiotherapy (RT). Abbreviations. UESL: undifferentiated embryonal sarcoma of the liver; CT: chemiotherapy; IRS: Intergroup Rhabdomyosarcoma Study; RT: radiotherapy; Anthr: anthracyclines; M: metastatic; T: tumor; L: local; N: nodal.

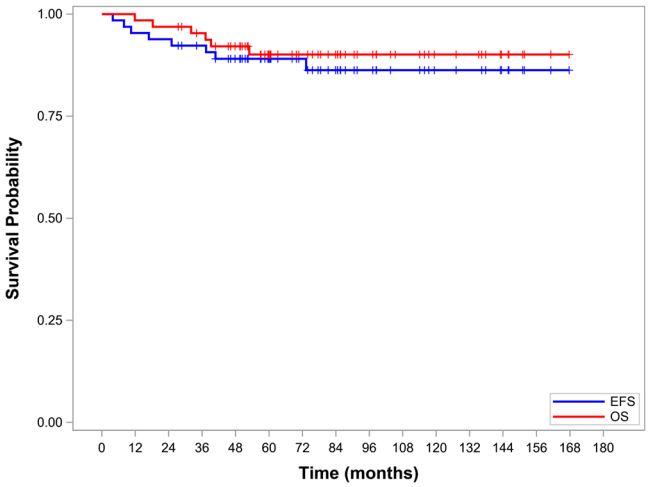

FIGURE 2 Event-free survival (EFS) and overall survival (OS) of patients treated for pediatric undifferentiated embryonal sarcoma of the liver.

(Table S4). None of the four patients with metastatic disease at diagnosis had relapse. At last follow-up, two patients (the patient with the second tumor, and one with a local relapse) were alive in second CR off therapy, and six died. The 5-year EFS is 89.1% (95% CI: 78.4–94.6) and the 5-year OS is 90.1% (95% CI: 79.2–95.5) (Figure 2).

The variables we tested in univariate analysis did not show a prognostic significance (Table 2). None of the variables tested for EFS showed to be associated with a *p*-value less than .20 for OS (unpublished data). Patients with delayed resection presented a nonsignificant trend toward a better outcome than those with upfront tumor resection. Two out four patients with local ± nodal or metastatic relapses had previous incomplete resections, and two out of three with exclusive metastatic relapses previously had reduced doses of alkylating agents.

4 | DISCUSSION

This study reports a series of prospectively registered pediatric patients treated in different European countries with a homogeneous strategy according to soft tissue sarcoma multimodal protocols. The 90% (95% CI: 79.2–95.5) survival rate represents an improvement in comparison to the original UESL series published by Stocker and Ishak and more recent series.[1,2] This confirms that the use of multimodal treatment has dramatically improved the EFS and OS for patients with UESL from 42% to 70%–90%.[1,3,7] This was also supported, at a larger scale, In the ARST0032 study, for intermediate grade NRSTS.[9] Multimodal therapies were also associated with the best OS in a large North American registry study.[7] Surgery forms the cornerstone of treatment for UESL as shown by a recent American registry study where complete surgery without chemotherapy resulted in good outcomes for a small subset (5%) of patients with localized UESL, although the combination of surgery plus chemotherapy was one of a few factors associated with better outcome.[7] In this North American study, the size (>15 cm) was identified as an OS prognosis factor in a multivariate analysis, which was not the case in our study including both EFS and OS. Looking at their statistical method, only the size-missing data fulfilled the criteria for multivariate analysis. Regarding this discrepancy, we advocate caution in interpreting size as a definitive prognosis

TABLE 2 EFS according to patient, tumor, and treatment characteristics.

	N	Events	5-year EFS (95% CI)	*p*-Value
Tumor invasiveness				
T1	50	5	89.9 (77.3–95.7)	.3870
T2	15	3	86.7 (56.4–96.5)	
IRS group				
I–II	23	5	82.6 (60.1–93.1)	.0938
III–IV	42	3	92.7 (78.9–97.6)	
Gender				
Female	23	2	91.1 (68.8–97.7)	.4278
Male	42	6	88.0 (73.5–94.8)	
Age				
<10 years	41	5	90.1 (75.8–96.2)	.8595
≥10 years	24	3	87.5 (66.1–95.8)	
Size				
<15 cm	35	4	88.6 (72.4–95.5)	.9880
>15 cm	26	3	92.3 (72.6–98.0))	
Chemotherapy				
With anthracyclines	47	4	93.5 (81.1–97.8)	.1181
Without anthracyclines	18	4	77.8 (51.1–91.0)	
Radiotherapy (RT)				
RT –	50	6	89.9 (77.3–95.7)	.8731
RT +	15	2	86.7 (56.4–96.5)	
Margins				
R0	51	5	90.1 (77.7–95.7)	.2738
R1/2	14	3	85.7 (53.9–96.2)	
Upfront surgery				
Yes	28	5	85.7 (66.3–94.4)	.2380
No	37	3	91.6 (76.2–97.2)	
Anatomical resection				
Yes	49	5	91.7 (79.5–96.8)	.3612
No	16	3	80.8 (51.4–93.4)	

Abbreviations: CI, confidence interval; EFS, event-free survival; IRS, Intergroup Rhabdomyosarcoma Study.

factor for UESL. Our European pediatric patients were enrolled in soft tissue sarcoma protocols that systematically used chemotherapy, and therefore there were no patients treated with surgical resection without chemotherapy. Response of UESL to chemotherapy is sometimes difficult to demonstrate on imaging as cystic components of the tumor do not reduce in size; however, histological examination of the resected mass demonstrates a high rate (80%–90%) of cell necrosis after chemotherapy.[2,4] Our analysis demonstrates that chemotherapy reduced tumor size in two-thirds of the patients, and delayed surgery resulted in negative margins more often than upfront surgery, confirming the findings of smaller studies.[4] There was a nonsignificant trend toward higher EFS and OS and a lower risk of tumor spillage in patients operated after neoadjuvant chemotherapy. This result is similar to the results published by the SIOP group for Wilms' tumor and hepatoblastoma compared to the North American approach of upfront surgical resection.[10,11] Similarly, the ARST00332 study focusing on NRSTS identified the risk of increased marginal resection rate with upfront compared to delayed resections, although without impact on survival.[9] The effects of primary versus delayed resection were not assessed in the North American study on UESL.[7] In the German group study, the margins were infiltrated in five of 12 primary resections versus two of eight delayed resections, although nonsignificant, due to an overall fewer number of patients compared to our study.[3] Primary resection does not reliably obtain negative margins of large tumors that tend to invade adjacent structures, may present with rupture, or may bleed. In the case of tumor spillage, postoperative treatment must be intensified, including abdominal irradiation, as happened in two of our patients.[4,7] Moreover, as two of the metastatic relapses occurred

in patients with R0 upfront resection (IRS I) without or with low alkylating agents (i.e., ifo/cyclophosphamide), there is no benefit in terms of chemotherapy burden for patients with upfront resections. Regarding the type of chemotherapy, most of the Europeans patients are treated with regimens including vincristine, D-actinomycin, and ifosfamide.[3] The role of anthracyclines, in our series, remains unclear as it was in successive protocols, although it was suggested to achieve a better response on unresectable big tumors.[12] The decision to give anthracyclines to seven out of nine IRS I patients was also surprising unless UESL was considered an unfavorable histology/location by the treating center. However, we did not find any differences in tumor response, EFS or OS, between those who received anthracyclines compared to those who did not, with the limitations of few numbers. Anthracyclines were widely used in our series and mainly given to IRS III–IV patients with tumors not amenable to upfront resection. Given the potential adverse events (cardiotoxicity and increased myelotoxicity), we cannot recommend the systematic use of this drug in localized UESL. In the North American ARSTS0032 study, in which there was a more systematic use of anthracyclines for these big and intermediate grade tumors, the study could not clarify the role of this drug in adjunction to ifosfamide.[9] The role of anthracyclines needs further investigation, possibly in patients with incomplete resection, tumor invasion of adjacent structures, lymph node disease (N1), or metastases. With the limitation of small patient numbers, we also warrant against removing alkylating agents (i.e., cyclo/Ifosfamide) from the treatment as two out of the three IRS I patients who presented with a metastatic relapse were treated with a limited cumulative dose of ifosfamide.

The role of RT remains to be established. In our study, 23.5% of patients received RT, which is similar to previous experience in which 12%–20% of patients received RT.[1–3,7,13] RT was mainly administered when there was evidence of tumor invasion into adjacent structures (patients with T2 tumor) or more often in the NRSTS 2005 protocol than in the MMT 95 protocol, this probably because a publication from 2000s identified this tumor with a bad prognosis, but we did not demonstrate an outcome advantage when RT was used.[2] The decision to administer RT as well as the selected dose level and the definition of target volume was not systematic, but rather was made by the treating center on an individual basis, resulting in small numbers, RT administration discrepancies in patients with infiltrated margins or spillage, and an inability to draw conclusions about its role.[3,7] In the majority of patients with UESL, and especially in those with T1-N0 tumors and negative surgical margins, we do not support the systematic use of RT, because of the potential radiation-induced liver disease.[14] It is worth underlining the favorable outcome of the few patients with metastatic disease in our study. This represents a major difference in comparison to the outcomes of metastatic patients with other types of sarcoma. In our series, only one patient required liver transplantation with a bad outcome; however, this approach in UESL has been shown in small series to have 78%–100% 5-year OS.[7,9,15] Given the morbidity of liver transplantation, it should only be considered in patients with remained unresectable UESL after neoadjuvant chemotherapy.[7]

Previous studies, although in fewer numbers, characterized the diagnosis features of UESLs: large (i.e., diameter >10 cm) tumors, with a cystic component, intratumoral bleeding, serpiginous vessels, or septa on IV tri-phase liver CT scans, and with normal alpha fetoprotein serum levels.[16] Once the diagnosis is suspected, a biopsy if safe (no bleeding or rupture) is mandatory to confirm the diagnosis, which is consistent with the PHITT trial (Clinicaltrial.gov: NCT03017326) and avoids diagnosis errors. Neoadjuvant chemotherapy and anatomical liver resection in expert hepatobiliary centers helped to obtain a radiological and pathological response with less infiltrated margins or spillage.[4] Future studies could assess both the role of surgical strategies with respect to the imaging studies like the pre-TEXT imaging classification for hepatoblastomas. In conclusion, this study demonstrates that an increasing number of patients with UESL can be cured with a combination of chemotherapy and surgical resection. After a biopsy to confirm the diagnosis, neoadjuvant chemotherapy with an alkylating agent (i.e., vincristine, cyclo or ifosfamide, and actinomycine)-based regimen increases the possibility of obtaining negative surgical margins and decreases tumor spillage. The role of anthracyclines and RT for localized disease requires further investigation, especially for patients with tumor extension into adjacent organs, infiltrated surgical margins, or tumor spillage.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

EXPECTS DATA SHARING

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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